ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF EFAVIRENZ EMPLOYING β-CYCLODEXTRIN, SOLUTOL HS15 AND PVP K30: A FACTORIAL STUDY

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ABSTRACT

Efavirenz, a widely prescribed anti retroviral drug belongs to class II under BCS and exhibits low and variable oral bioavailability due to its poor aqueous solubility. It is practically insoluble in water and aqueous fluids. As such its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. The objective of the study is to evaluate the individual main effects and combined (or interaction) effects of β cyclodextrin (βCD), Solutol HS15 (surfactant) and PVP K30 on the solubility and dissolution rate of efavirenz in a series of 2-factorial experiments. The solubility of efavirenz in eight selected fluids containing βCD, Solutol HS15 and PVP K30 as per 23 factorial experiments. The solubility of efavirenz increased in the presence of βCD and the highest solubility enhancement was observed in the presence of βCD, Solutol HS15 and PVP K30. The combination of βCD with Solutol HS15 and PVP K30 resulted in a much higher enhancement in the solubility of efavirenz, 16.86 fold with βCD- Solutol HS15 and 6.86 fold with βCD- PVP K30. Solid inclusion complexes of efavirenz-βCD were prepared with and without Solutol HS15 and PVP K30 by kneading method as per 22 factorial design and were evaluated. ANOVA indicated that the individual main effects of βCD, Solutol HS15 and PVP K30 and their combined effects in enhancing the solubility and dissolution rate (K1) were highly significant (P < 0.01). Combination of βCD with Solutol HS15 and PVP K30 also gave significantly higher dissolution rates (K1) when compared to βCD alone. βCD alone gave 3.55 fold increase and in combination with Solutol HS15 and PVP K30, it gave respectively 8.59 and 5.92 fold increase in the dissolution rate of efavirenz. Solutol HS15 and PVP K30 alone and in combination also gave respectively 7.54, 3.92 and 7.08 fold increase in the dissolution rate of efavirenz. Hence a combination of βCD with Solutol HS15 and/or PVP K30 or Solutol HS15 and PVP K30 alone is recommended to enhance the solubility and dissolution rate of efavirenz a BCS class II drug.

Keywords: Efavirenz, β Cyclodextrin, Solutol HS15, PVP K30, Solubility, Dissolution rate, Factorial Study.

INTRODUCTION

Efavirenz, a widely prescribed HIV-1 specific non – nucleoside reverse transcriptase inhibitor drug belongs to class II under BCS and exhibits low and variable oral bioavailability due to its poor aqueous solubility. It is practically insoluble in water and aqueous fluids. As such its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. Several techniques such as micronization, cyclodextrin complexation, use of surfactants and solubilizers, solid dispersion in water soluble and dispersible carriers, use of salts, prodrugs and polymorphs which exhibit high solubility, micro emulsions and self emulsifying micro and nano dispense systems have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble drugs. Among the various approaches complexation with cyclodextrins has gained good acceptance in recent years in industry for enhancing the solubility and dissolution rate of poorly soluble drugs. Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and a lipophilic central cavity which can accommodate a variety of lipophilic drugs. As a consequence of inclusion process many physico-chemical properties such as solubility, dissolution rate, stability and bioavailability can be favourably affected. Cyclodextrins have been receiving increasing application in pharmaceutical formulation in recent years due to their approval by various regulatory agencies. Solutol HS15 (polyethylene glycol(60-12-hydroxy stearate) is a non-ionic surfactant used for pharmaceutical purposes produced from 1 mol 12-hydroxy stearic acid and 15 mol ethylene oxide. The product is very efficient in solubilising substances like fat-soluble vitamins, and active ingredients of hydrophobic nature. Solutol HS15 is approved by the HPB (Canada) for human application. Solutol HS15 has been used to enhance the solubility of insoluble drugs such as nifedipine and paclitaxel and as carrier in solid dispersions for increasing the dissolution rate and bioavailability of poorly soluble drugs such as curcumin and biochanin A. Poly vinyl pyrrolidone (PVP K30) is also reported to enhance the solubility and dissolution rate of poorly soluble drugs.

Though cyclodextrin complexation and use of surfactants and PVP for enhancing the solubility and dissolution rate of poorly soluble drugs have been investigated individually, no reports are available on their combined use in enhancing the solubility and dissolution rate. In the present investigation the individual main effects and combined (or interaction) effects of β cyclodextrin (βCD), Solutol HS15 (surfactant) and PVP K30 on the solubility and dissolution rate of efavirenz, a BCS class II drug were evaluated in a 23 factorial study.

MATERIALS AND METHODS

Materials

Efavirenz was a gift sample from M/s. Eisai Pharma technology and Manufacturing Pvt. Ltd., Visakhapatnam. β Cyclodextrin was gift sample from M/s. Cerestar Inc., USA. Methanol (Qualigens), poly vinyl pyrrolidone (PVP K30) and Solutol HS15 were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Methods

Estimation of Efavirenz

A UV Spectrophotometric method based on the measurement of absorbance at 245 nm in water containing 2 % Sodium lauryl sulphate (SLS) was used for the estimation of efavirenz. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer’s law in the concentration range of 0-10 µg/ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 1.12% and 0.95% respectively. No interference by the excipients used in the study was observed.

Solubility Determination

Excess drug (50 mg) was added to 15 ml of each fluid taken in 25 ml stopped conical flask and the mixtures were shaken for 24 h at room temperature (28±1°C) on Rotary Flask Shaker. After 24 h of shaking, 2 ml aliquots were withdrawn at 2 h interval and filtered immediately using a 0.45 µm filter. The filtered samples were diluted suitably and assayed for efavirenz by measuring absorbance at 245 nm. Shaking was continued until two consecutive estimations are the same. The solubility experiments were replicated four times each (n=4).
Preparation of Efavirenz - βCD Complexes

Solid inclusion complexes of efavirenz - βCD - Solutol HS15 - PVP K30 were prepared as per 2²-factorial study by kneading method. Efavirenz, βCD, Solutol HS15 and PVP K30 were triturated in a mortar with a small volume of solvent consisting of a blend of water: methanol (1:1). The thick slurry formed was kneaded for 45 min and then dried at 55°C until dry. The dried mass was powdered and sieved to mesh No. 120.

Dissolution Rate Study

The dissolution rate of efavirenz as such and from βCD complexes were studied in 900 ml water containing 2 % Sodium lauryl sulphate (SLS) using Disso 2000 (Labindia) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature 37±1°C was maintained throughout the study. Efavirenz or efavirenz - βCD complex equivalent to 100 mg of efavirenz was used in each test. Samples of dissolution media (5 ml) were withdrawn through a filter (0.45 µ) at different intervals of time, suitable diluted and assayed for efavirenz at 245 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh fluid and a suitable correction has been applied in calculating the percent drug dissolved at various times. The dissolution experiments were replicated three times each (n=3).

Table 1: Solubility of Efavirenz in Various Fluids as per 2³-Factorial Study

<table>
<thead>
<tr>
<th>Fluids (Code as per 2³-Factorial Experiment)</th>
<th>Solubility (mg/ml) (n=4)</th>
<th>Increase in Solubility (Number of Folds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distilled water (1)</td>
<td>0.14 (1.1)</td>
<td>-</td>
</tr>
<tr>
<td>Water containing 5 mM βCD (a)</td>
<td>0.48 (1.2)</td>
<td>3.42</td>
</tr>
<tr>
<td>Water containing 2% Solutol HS15 (b)</td>
<td>1.24 (1.1)</td>
<td>8.56</td>
</tr>
<tr>
<td>Water containing 5 mM βCD and 2% Solutol HS15 (ab)</td>
<td>2.36 (1.2)</td>
<td>16.86</td>
</tr>
<tr>
<td>Water containing 2% PVP (c)</td>
<td>0.74 (0.8)</td>
<td>5.29</td>
</tr>
<tr>
<td>Water containing 5 mM βCD and 2% PVP (ac)</td>
<td>0.96 (0.9)</td>
<td>6.86</td>
</tr>
<tr>
<td>Water containing 2% Solutol HS15 and 2% PVP (bc)</td>
<td>1.68 (1.4)</td>
<td>12</td>
</tr>
<tr>
<td>Water containing 5 mM βCD, 2% Solutol HS15 and 2% PVP (abc)</td>
<td>2.68 (0.9)</td>
<td>19.14</td>
</tr>
</tbody>
</table>

The solubility data were subjected to Analysis of Variance (ANOVA) to find out the significance of main and combined effects of βCD, Solutol HS15 and PVP K30 on the solubility of efavirenz. The results of ANOVA indicated that the individual and combined effects of βCD, Solutol HS15 and PVP K30 in enhancing the solubility of efavirenz were highly significant (P < 0.01). βCD alone gave a 3.42 fold increase in the solubility of efavirenz. Combination of βCD with Solutol HS15 and PVP K30 resulted in a much higher enhancement in the solubility of efavirenz, 16.86 fold with βCD- Solutol HS15 combination and 6.86 fold with βCD- PVP K30 combination than with βCD alone. Solutol HS15 and PVP K30 alone also gave a significant enhancement, 8.56 and 5.29 fold respectively in the solubility of efavirenz. Among the three factors Solutol HS15 (factor B) gave highest enhancement (8.56 fold) in the solubility of efavirenz. Among all, combination of the three factors (i.e. treatment abc) gave highest enhancement (19.14 fold) in the solubility of efavirenz.

To evaluate the individual and combined effects of βCD, Solutol HS15 and PVP K30 on the dissolution rate of efavirenz, solid inclusion complexes of efavirenz- βCD were prepared with and without Solutol HS15 and PVP K30 as per 2²-factorial design. For this purpose two levels of βCD (0 and 1:2 ratio of drug : βCD) and two levels of each of Solutol HS15 and PVP K30 (0 and 2%) were selected and the corresponding eight treatments involved in the 2²-factorial study were efavirenz pure drug (1); efavirenz- βCD (1:2) inclusion binary complex (a); efavirenz - Solutol HS15 (2%) binary complex (b); efavirenz - βCD (1:2) - Solutol HS15 (2%) ternary complex (ab); efavirenz – PVP K30 (2%) binary complex (c); efavirenz - βCD (1:2) - PVP K30 (2%) ternary complex (ac); efavirenz - Solutol HS15 (2%) - PVP K30 (2%) ternary complex (bc) and efavirenz-βCD (1:2) - Solutol HS15 (2%) - PVP K30 (2%) complex (abc).

The CD complexes were prepared by kneading method. All the solid inclusion complexes of efavirenz- βCD - Solutol HS15 - PVP K30 prepared were found to be fine and free flowing powders. Low coefficient of variation (c.v.) values (< 1.2%) in the percent drug content indicated uniformity of drug content in each batch of solid inclusion complexes prepared. The dissolution rate of efavirenz alone and from βCD complexes was studied in water containing 2 % SLS as prescribed in IP 2010. The dissolution of efavirenz followed first order kinetics with r (correlation coefficient) above 0.9210.

Analysis of Data

Solubility and dissolution data were analyzed by Analysis of Variance (ANOVA) as per 2²-factorial study.

RESULTS AND DISCUSSION

The individual main effects and combined (interaction) effects of βCD (Factor A), Solutol HS15 (Factor B) and PVP K30 (Factor C) on the aqueous solubility of efavirenz were evaluated in a series of 2²-factorial experiments. For this purpose, two levels of βCD (0, 5 mM), two levels of Solutol HS15 (0, 2%) and two levels of PVP K30 (0, 2%) were selected in each case and the corresponding eight treatments involved in the 2²-factorial study were purified water (1); water containing 5 mM βCD (a); water containing 2% Solutol HS15 (b); water containing 5 mM βCD and 2% Solutol HS15 (ab); water containing 2% PVP K30 (c); water containing 5 mM βCD and 2% PVP K30 (ac); water containing 2% Solutol HS15 and 2% PVP K30 (bc) and water containing 5 mM βCD and 2% of each of Solutol HS15 and PVP K30 (abc).

The solubility of efavirenz in the above mentioned fluids was determined (n=4) and the results are given in Table-1.

Table 2: Dissolution Parameters of Efavirenz – βCD - Solutol HS15 - PVP K30 Inclusion Complexes Prepared as per 2²-Factorial Study

<table>
<thead>
<tr>
<th>EF – CD Complex</th>
<th>Composition</th>
<th>PD10 (%)</th>
<th>Kx x 10⁸ (min⁻¹)</th>
<th>Increase in K1 (no. of folds)</th>
<th>DE₃₀ (%)</th>
<th>Increase in DE₃₀ (no. of folds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>EF</td>
<td>23.49</td>
<td>1.45</td>
<td>-</td>
<td>30.6</td>
<td>-</td>
</tr>
<tr>
<td>Pᵤ</td>
<td>EF- βCD (1:2)</td>
<td>58.30</td>
<td>5.15</td>
<td>3.55</td>
<td>66.4</td>
<td>2.16</td>
</tr>
<tr>
<td>Pᵤ</td>
<td>βCD (1:2) - Solutol HS15 (2%)</td>
<td>80.90</td>
<td>10.94</td>
<td>7.54</td>
<td>82.4</td>
<td>2.69</td>
</tr>
<tr>
<td>Fₛ</td>
<td>EF – Solutol HS15 (2%)</td>
<td>89.58</td>
<td>12.45</td>
<td>8.59</td>
<td>89.56</td>
<td>2.93</td>
</tr>
<tr>
<td>Fₛ</td>
<td>βCD (1:2) - Solutol HS15 (2%)</td>
<td>62.4</td>
<td>5.68</td>
<td>3.92</td>
<td>72.40</td>
<td>2.37</td>
</tr>
<tr>
<td>Fₛ</td>
<td>βCD (1:2) - PVP (2%)</td>
<td>78.3</td>
<td>8.59</td>
<td>5.92</td>
<td>76.69</td>
<td>2.51</td>
</tr>
<tr>
<td>Fₛ</td>
<td>βCD (1:2) - Solutol HS15 (2%) – PVP (2%)</td>
<td>86.4</td>
<td>10.28</td>
<td>7.08</td>
<td>86.2</td>
<td>2.82</td>
</tr>
<tr>
<td>Fₛ</td>
<td>βCD (1:2) - Solutol HS15 (2%) – PVP (2%)</td>
<td>88.6</td>
<td>12.65</td>
<td>8.72</td>
<td>90.2</td>
<td>2.94</td>
</tr>
</tbody>
</table>

The dissolution of efavirenz was rapid and higher in the case of efavirenz - βCD binary and ternary complex systems prepared when compared to efavirenz pure drug as such. The dissolution profiles are given in Fig-1.
The dissolution rate ($K_1$) values were subjected to ANOVA to find out the significance of the main and combined effects of βCD, Solutol HS15 and PVP K30 on the dissolution rate of efavirenz. ANOVA indicated that the individual main effects of βCD, Solutol HS15 and PVP K30 and their combined effects in enhancing the dissolution rate ($K_1$) were highly significant ($P < 0.01$). βCD alone gave a 3.55 fold increase in the dissolution rate of ($K_1$) of efavirenz. When βCD is combined with Solutol HS15 and PVP K30 the dissolution rate ($K_1$) was significantly enhanced. An 8.59 and 5.92 fold increase in the dissolution rate ($K_1$) was observed respectively with efavirenz - βCD - Solutol HS15 and efavirenz- βCD - PVP K30 solid inclusion complexes. Solutol HS15 (F$_a$) and PVP K30 (F$_b$) alone and in combination (F$_{ab}$) also gave respectively 7.54, 3.92 and 7.08 fold increase in the dissolution rate ($K_1$) of efavirenz. DE$_a$ values were also much higher in the case of βCD – Solutol HS15 – PVP K 30 solid complexes when compared to efavirenz pure drug. Combination of the three factors (treatment abc) gave highest enhancement in the dissolution rate (8.72 fold) of efavirenz and is compared with them alone. The higher dissolution rates observed with combination of βCD with Solutol HS15 and / or PVP K30 is due to better inclusion / entrapment of drug in the βCD molecules in the presence of Solutol HS15 and PVP K30.

CONCLUSIONS

1. The individual and combined effects of βCD, Solutol HS15 and PVP K30 in enhancing the solubility and dissolution rate of efavirenz were highly significant ($P < 0.01$).

2. βCD alone gave a 3.42 fold increase in the solubility of efavirenz. Combination of βCD with Solutol HS15 and PVP K30 resulted in a much higher enhancement in the solubility of efavirenz, 16.86 fold with βCD- Solutol HS15 and 6.86 fold with βCD- PVP K30 complexes. 3. Combination of βCD with Solutol HS15 and PVP K30 also gave significantly higher dissolution rates ($K_1$) when compared to βCD alone.

3. βCD alone gave 3.55 fold increase and in combination with Solutol HS15 and PVP K 30, it gave respectively 8.59 and 5.92 fold increase in the dissolution rate of efavirenz.

4. Solutol HS15 and PVP K30 alone also gave a higher enhancement in the solubility and dissolution rate of efavirenz.

5. Hence a combination of βCD with Solutol HS15 and / or PVP K30 or Solutol HS15 and PVP K30 alone is recommended to enhance the solubility and dissolution rate of efavirenz a BCS class II drug.

REFERENCES


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